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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,432	11/10/2003	Wojtek Auerbach	REG 784	4884
26693 7590 06/05/2007 REGENERON PHARMACEUTICALS, INC 777 OLD SAW MILL RIVER ROAD TARRYTOWN, NY 10591			EXAMINER MONTANARI, DAVID A	
			ART UNIT 1632	PAPER NUMBER
			MAIL DATE 06/05/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/705,432

Applicant(s)

AUERBACH ET AL.

Examiner

David Montanari

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>2/27/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicants arguments and amendment filed 2/27/2007 have been entered.
2. Claims 17, 21, 25 and 29 are amended.
3. Claims 17-32 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 17, 21, 25 and 29 have been amended to recite the term “pre-selected” to replace the term “specific”. Applicants argue in amendment filed 2/27/07 that the phrase “pre-selected chromosomal location” is identical in scope with the phrase “specific chromosomal location”, and that this amendment is not one of patentability but to underscore the fact that a specific chromosomal location has been pre-selected. These arguments are not persuasive. The scope of “specific” and “pre-selected” are different. Further, Applicants do not point out where in the instant specification support exists for the term “pre-selected” and currently the Examiner cannot find this support. The term pre-selected possesses the step that the skilled artisan made a

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determination at some prior point in time to target a chromosomal location. Whereas the term specific means any identified chromosomal location at any time can be chosen. These scopes are not the same and thus a new matter rejection is necessitated.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes “If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes “When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not “new matter” is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 17-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rohozinski et al. (Genesis, 2002, Vol. 32, pgs. 1-7) in view of Tsirigotis et al. (BioTechniques, 2001, Vol. 31, pgs. 120-130) and Ghazizadeh et al. (J. Invest. Dermat., 1998 Vol. 111, pgs. 492-496) for reasons of record in the office action mailed 8/28/2006.

Claims 17-32 are drawn to an *in vitro* method of targeting a targeting vector into mouse embryonic stem (ES) cell, comprising introducing into said ES cells a targeting vector comprising a ubiquitin promoter, wherein the targeting vector comprises a drug resistance gene encoding neomycin phosphotransferase, hygromycin phosphotransferase, or puromycin acetyl transferase under control of a ubiquitin promoter, wherein said promoter is the ubiquitin C promoter that is a human, mouse, rat, or bacterial ubiquitin C promoter.

Response to Arguments

Applicants argue in amendment filed 2/27/07 that cited references above, when combined do not render the claimed method obvious. Applicants have summarized the above references in detail, pointing to the specific teachings in each reference. Applicants argue that a careful analysis of the cited references shows that none of them in any combination discloses or suggests methods for targeting genes to a pre-selected locus in a genome using a targeting vector comprising a ubiquitin promoter operably linked to a drug resistance gene. Applicants argue

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along five points of reasoning that the disclosed references should not be used: 1) that the Examiner provided no reasonable scientific rationale or motivation to combine the cited references, 2) a fair reading of the references reveals that they should not be combined, 3) even if the references are combined they do not add up to the present invention, 4) the Examiner used impermissible hindsight analysis in conjunction with an impermissible “obvious to try” standard and 5) regardless of what the cited references teach the claimed invention resulted from unexpected results. None of the arguments are persuasive.

Carefully examining claim 17, the claim requires a mouse ES cell that has had a targeting vector introduced. This targeting vector comprises a drug resistance gene under control of the ubiquitin promoter and homology arms. Homology arms do only one thing, they target nucleotides in the chromosome. That is their nature and their purpose. Applicants have given significant weight to the preamble in the method claims to argue that the cited references should not be used and/or combined. However this is not the case for the purposes of applying art in this instance. It is immediately obvious to the ordinary artisan that homology arms are the means to target nucleotide regions in the genome, and the art teaches this. Further ample motivation is provided that using the ubiquitin promoter would be a great decision in this case as well, and that using a drug resistance gene would also be good for selecting cells. Applicants have argue in detail that none of these references would lead the ordinary artisan to target a “specific” or now “pre-selected” chromosomal location, but using homology arms do this inherently, and this have been done for many years in molecular biology. The method only comprises putting into mouse ES cells a targeting vector wherein the vector comprises a ubiquitin promoter driving any drug resistance gene and homology arms. The art of record clearly teaches each of these elements and

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further motivates the ordinary artisan to do so. Thus for reasons of record and above the rejection is maintained.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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